## DETAILED ACTION

**The examiner of record has changed. Please address all future correspondence to Examiner Mummert, whose contact information has been included at the conclusion of this action.**

### *Election/Restrictions*

Applicant's election without traverse of Group I, claims 28-44 and 46 in the reply filed on January 18, 2008 is acknowledged.

Claims 45 and 47-53 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on January 18, 2008.

Claims 28-44 and 46 are pending and will be examined.

A further species election was made over the structures of claims 43 and 44. Applicant agreed to elect species Y2 (claim 43) and Y'2 (claim 44) for further search and examination during a telephone conversation with Justine Wilbur on March 13, 2008.

### *Information Disclosure Statement*

The information disclosure statement (IDS) submitted on May 31, 2005 was filed in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 28, 30-42 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van Ness et al. (US Patent 5,232,830; August 1993) in view of Lee et al. (J. Agr. Food Chem., 1999, vol. 47, p. 2766-2770). Van Ness teaches a method of detection of target analytes using a capture member immobilized on a solid support and determining fluorescence (Abstract).

With regard to claim 28, Van Ness teaches a method for detection of an analyte a in a fluid sample, comprising the following steps:

1) saturating a solid support comprising, on at least part of its surface, at least one trifunctional reagent (tripod Y) (col. 5, lines 56 to col. 6, lines 9, where the capture molecule or receptor is attached through a multifunctional reagent attached to a solid support and includes a

heterotrifunctional reagents) comprising the following three functional poles:

i) a luminescent group (L) (col. 5, lines 17-22, where the solid support comprises luminescence inherently);

ii) a molecule (B) selected from the group consisting of the analyte a (col. 4, lines 14-23, where the capture member is contacted with a ligand pair, or an analyte; col. 3, lines 18-25), an analog of the analyte a or a fragment of the analyte a; and

iii) a function that provides attachment of the trifunctional reagent to the surface of the solid support (col. 5, line 56 to col. 6, line 9, where the multifunctional reagents are attached by a preferred amine group);

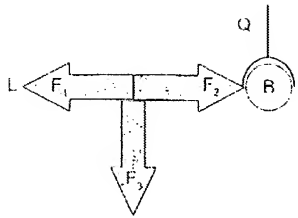
2) bringing the solid support obtained in step 1) into contact with a fluid sample that may comprise the analyte a to be detected (col. 10, where the detection of an analyte in a biological sample is disclosed).

With regard to claim 31, Van Ness teaches an embodiment of claim 28, wherein the solid support is selected from the group consisting of glasses, plastics, ceramics, metals and metalloids (col. 3, lines 54-68, where the solid support consists of plastics and glasses).

With regard to claim 32, Van Ness teaches an embodiment of claim 28, wherein the solid support is in the form of a tube, a capillary, a plate or a bead (col. 3, lines 25-30, where the solid support comprises beads, membranes, wells, plastic strips; lines 54-68).

With regard to claim 33, Van Ness teaches an embodiment of claim 28, wherein the fluid sample consists of water, a liquid biological medium, or a liquid medium comprising dissolved gaseous molecules or molecules originating from solid samples (col. 10, where the detection of an analyte in a biological sample is disclosed).

With regard to claim 35, Van Ness teaches an embodiment of claim 28, wherein the complex C formed at the end of the saturation in 1 ) is selected from the group consisting of complexes of formula (I) below:



(I)

wherein:

- the arrows represent the structure of the backbone of the tripod Y, which is a linker arm consisting of a peptide, nucleotide or glucoside chain or of a saturated or unsaturated, linear or branched hydrocarbon-based chain; the chains being optionally substituted, interrupted and/or ended with one or more hetero atoms, such as N, O or S, and/or with one or more amino acids, and comprising three reactive chemical functions F1, F2 and F3 (col. 5, line 56 to col. 6, line 9, where the multifunctional reagents are attached by a preferred amine group and where the multifunctional reagent comprises heterotrifunctional reagents);

the molecule (B) being covalently bonded to the tripod Y by the reactive chemical function F2 (col. 5, line 56 to col. 6, line 9, where the multifunctional reagents are attached by a preferred amine group and where the multifunctional reagent comprises heterotrifunctional reagents, and

where the molecule B, which in this case comprises an oligonucleotide, is attached to the functional group on the multifunctional reagent);

- L represents a luminescent group covalently bonded to the tripod Y by the reactive chemical function F1 (col. 5, line 56 to col. 6, line 9, where the multifunctional reagents are attached by a preferred amine group);

- F3 represents a reactive chemical function that can allow the attachment of the tripod Y to the surface of the solid support (col. 5, line 56 to col. 6, line 9, where the multifunctional reagents are attached by a preferred amine group).

With regard to claim 36, Van Ness teaches an embodiment of claim 35, wherein the functions Fl, F2 and F3, independently of one another, provide:

i) either a direct linkage via a corresponding chemical function present on the luminescent compound, the molecule (B) or the solid phase (col. 5, line 56 to col. 6, line 9, where the multifunctional reagents are attached by a preferred amine group);

ii) or an indirect linkage, and in this case, the linkage is carried out by coupling, to at least one of the functions F1, F2 and/or F3, a molecule M1 forming a complex with a molecule M2 attached beforehand to at least part of the surface of the solid phase, to the molecule (B) and/or to the luminescent group (col. 4, lines 14-23, where the capture member is contacted with a ligand pair, or an analyte; col. 3, lines 18-25).

With regard to claim 37, Van Ness teaches an embodiment of claim 35, wherein the functions F1, F2 and F3, which may be identical or different, are selected from the group consisting of: thiols; amines; alcohols; acid functions; esters; isothiocyanates; isocyanates; acylazides; sulfonyl chlorides; aldehydes; glyoxals; epoxides; oxiranes; carbonates; imidoesters;

carbodiimides; maleimides; nitriles; aziridines; acryloyl; halogenated derivatives; disulfide groups; phosphorus-containing groups; diazo; carbonyldiimidazole; hydrazides; arylazides; hydrazines; diazirines; magnesium compounds; lithium compounds; cuprates; zinc compounds and unsaturated systems (col. 5, line 56 to col. 6, line 9, where the multifunctional reagents are attached by a preferred amine group).

With regard to claim 38, Van Ness teaches an embodiment of claim 37, wherein the functions F1, F2 and F3 are selected from the group consisting of amine functions of formulae R- NH2, R-NH-, (R)3-N, R-NH-OR and NH2-OR; alcohol functions R-OH; and halogenated groups of formula R-X with X representing a halogen atom; it being understood that, in tile formulae, R represents an alkyl, aryl, vinyl or allyl radical (?).

With regard to claim 46, Van Ness teaches a method for continuous heterogeneous-phase detection of an analyte a in a fluid sample, comprising detecting the analyte a in a fluid sample with at least one complex C of formula (I) (col. 10, where the detection of an analyte in a biological sample is disclosed).

Regarding claim 28, VanNess does not teach that receptor was labeled with a compound that quenches luminescence. Lee teaches a homogeneous method of immunoassay for the detection of an analyte, however, Lee also teaches that the interaction and competition between a quenched reporter and a luminescent pseudo-antigen results in detection of the target analyte (Abstract).

With regard to claim 28, Lee teaches a luminescent group (L) (Abstract, p. 2768, 'labeling of Ag' heading, where the antigen is associated with an amine reactive fluorescein dye, FITC), ii) a molecule (B) selected from the group consisting of the analyte a, an analog of the

analyte a or a fragment of the analyte a (p. 2768, col. 2, 'labeling of Ag' heading, where the antigen is the analyte; see also p. 2767, col.1); and a receptor for the analyte a, the receptor being labeled with a compound (Q) (receptor-Q) that quenches the huninescence of the group L (p. 2767, col. 2, 'labeling of Ab' heading, where the antibody receptor is labeled with a TMR-SE; p. 2767, col. 1, where when the antibody binds to labeled antigen, fluorescence quenching occurs), so as to form a complex C between the molecule (B) and the receptor-Q (p. 2767, col. 1, where when the antibody binds to labeled antigen, fluorescence quenching occurs);
3) measuring the intensity of the signal emitted by the group L, which is proportional to the amount of analyte a present in the fluid sample (p. 2768, 'fluorescence excitation transfer measurements' heading; p. 2767, col. 1, where when the antibody/receptor binds to labeled antigen/analyte, fluorescence quenching occurs, when sample containing analyte is added unlabeled analyte/antigen competes for the receptor/antibody site and the amount of fluorescence quenching is reduced in proportion to the concentration of analyte in the sample); and
4) regenerating the solid support by bringing the solid support into contact with the receptor-Q (p. 2769, col. 2, 'conclusions' heading, where fluorescence was restored after adding excess spinosyn A to the reaction solution).

With regard to claim 30, Lee teaches an embodiment of claim 28, wherein step 3) and step 4) are carried out continuously (p. 2768, 'fluorescence excitation transfer measurements' heading).

With regard to claim 34, Lee teaches an embodiment of claim 28, wherein the intensity of the signal emitted during step 3) is determined by a luminescence detector (p. 2768, col.

'fluorescence excitation transfer measurements' heading, where the signal is measured using a fluorometer).

With regard to claim 35, Lee teaches components of the structure of complex C, comprising:

-B represents an analyte a, a structural analog of an analyte a or a fragment of an analyte a to which is noncovalently and reversibly attached a receptor specific for the analyte a, the receptor being labeled with a compound Q (p. 2768, 'fluorescence excitation transfer measurements' heading; p. 2767, col. 1, where when the antibody/receptor binds to labeled antigen/analyte, fluorescence quenching occurs; p. 2767, where the antibody/receptor is labeled with a quencher, Q);

- Q represents a compound that quenches the luminescence of the group L (p. 2768, 'fluorescence excitation transfer measurements' heading; p. 2767, col. 1, where when the antibody/receptor binds to labeled antigen/analyte, fluorescence quenching occurs; p. 2767, where the antibody/receptor is labeled with a quencher, Q).

With regard to claim 39, Lee teaches an embodiment of claim 28, wherein the luminescent group is selected from the group consisting of fluorescein and its derivatives; rhodamine and its derivatives; diaminidophenyl indo; acridine; fluorescent dyes with reactive amines; eosin; and erythrosine (p. 2768, 'labeling of Ag' heading, where the antigen or analyte is labeled with amine reactive fluorescein dye, FITC).

With regard to claim 40, Lee teaches an embodiment of claim 28, wherein the receptor is selected from the group consisting of antibodies in whole, fragmented or recombinant form, biological receptors, nucleic acids, peptide nucleic acids, lectins, transporter proteins, chelates

and synthetic receptors (Abstract, p. 2767, col. 1, where the receptor comprises an antibody labeled with a quencher).

With regard to claim 41, Lee teaches an embodiment of claim 28, wherein the receptor exhibits greater affinity for the analyte a than for the molecule (B) (p. 2767, col. 1).

With regard to claim 42, Lee teaches an embodiment of claim 28, wherein the quenching compound (Q) is selected from the group consisting of rhodamine and its derivatives, the fluorescent compounds mentioned in claim 12, and nonfluorescent molecules (p. 2767, col. 2, 'labeling of Ab' heading, where the antibody is reacted through an amine reactive reagent, TMR-SE; which is a rhodamine derivative).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have applied the competitive quenched format of detection taught by Lee to the solid phase receptor based format of immunoassay taught by Van Ness to arrive at the claimed invention with a reasonable expectation for success. While Lee teaches the luminescent group is attached to the molecule B or analyte, the combination of the multifunctional group in the method of Van Ness, the presence of the fluorescence group of Van Ness on the support, the proximity between the label and quencher as taught by Lee achieves a format wherein the support is quenched prior to assay, followed by competition with an unlabeled analyte overcoming the quenching leading to increase in signal which is proportional to the amount of analyte in the sample. Therefore, it would have been prima facie obvious to achieve the method of the instant invention through a combination of Van Ness and Lee. As taught by Lee, "when sample Ag is introduced into solution, competition for the Ab binding sites occurs between the nonlabeled sample Ag and labeled Ag, and the amount of fluorescence quenching will be

reduced in proportion to the concentration of nonlabeled Ag" (p. 2767, col. 1). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have applied the competitive quenched format of detection taught by Lee to the solid phase receptor based format of immunoassay taught by Van Ness to arrive at the claimed invention with a reasonable expectation for success.

Claim 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over Van Ness et al. (US Patent 5,232,830; August 1993) in view of Lee et al. (J. Agr. Food Chem., 1999, vol. 47, p. 2766-2770) as applied to claims 28, 30-42 and 46 above and further in view of Plowman et al. (Analytical Chemistry, 1999, vol. 71, p. 4344-4352). Van Ness teaches a method of detection of target analytes using a capture member immobilized on a solid support and determining fluorescence (Abstract).

Regarding claim 29, Van Ness teaches tripods Y (col. 5, lines 56 to col. 6, lines 9, where the capture molecule or receptor is attached through a multifunctional reagent attached to a solid support and includes a heterotrifunctional reagents). However, neither Van Ness nor Lee teach multiple types of tripods or the detection of multiple analytes.

With regard to claim 29, Plowman teaches an embodiment of claim 28, wherein several types of tripods Y that differ from one another through the nature of the molecule (B) that they comprise are attached to distinct and known zones of the solid support (Abstract, Figure 1, Table 2, where the method is applied to the detection of multiple analytes and therefore different formats of the reagent attached to the solid support).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have applied the detection of multiple targets as taught by Plowman to the method of detection taught by Van Ness and Lee to arrive at the claimed invention with a reasonable expectation for success. As taught by Plowman, "Multiple analyte immunoassay (MAIA) results for two sets of three different analytes, one employing polyclonal and the other monoclonal capture antibodies, where compared with the results for identical analytes performed in a single analyte immunoassay (SAIA) format" (Abstract). Plowman therefore teaches the detection and analysis of multiple analytes in an immunoassay format similar in practice to the methods of Van Ness and Lee. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have applied the detection of multiple targets as taught by Plowman to the method of detection taught by Van Ness and Lee to arrive at the claimed invention with a reasonable expectation for success.

***Pertinent Prior Art***

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Miyazaki et al. (US Patent 5,229,302; July 1993) teaches a fluorescence immunoassay wherein the presence of analyte increases fluorescence that was previously quenched (Abstract). Ballerstadt et al. (Analytica Chimica Acta, 1997, vol. 345, p. 203-212) teaches a fluorescence quenching affinity assay for the detection of lectins (Abstract).

***Conclusion***

Claims 43 and 44 are free of the prior art. A thorough search of the prior art of the specific elected structure, Y2 and Y'2 was conducted and there was no disclosure in the prior art of the specifically elected structure. While the prior art teaches multifunctional reagents, the specific structure is not disclosed and would not have been an obvious structure based on the more general teachings in the prior art.

Claims 43 and 44 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 28-42 and 46 stand rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEPHANIE K. MUMMERT whose telephone number is (571)272-8503. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Stephanie K. Mummert/
Patent Examiner, Art Unit 1637

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